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## Sonic Hedgehog signalling in the developing and adult brain.

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Sonic Hedgehog (Shh) belongs to a family of secreted polypeptides implicated in embryonic development. Shh displays inductive, proliferative, neurotrophic and neuroprotective activities on various neural cells and signals through a receptor complex associating Patched (Ptc) and Smoothened (Smo). Shh binding to Ptc leads to downstream activation of target genes, such as transcription factors of the Gli family. We have investigated the distribution of Shh signalling genes in the rat embryo and in the adult, as well as pharmacological properties of Shh peptides. In the ventral neural tube, the distribution of Shh, Ptc and Smo is in agreement with this functional model. In the postnatal cerebellum, Shh expressed by Purkinje cells may act on its target receptor complex localized in the external germinative layer to activate Gli1. Myristoylated ShhN (myrShhN) is more potent than ShhN in stimulating proliferation of rat cerebellar granule cell neuroblasts in culture, as evaluated by [3H]thymidine incorporation, suggesting that amino terminal lipid modification of the molecule plays a crucial role in ShhN biological activity. In the adult brain, Ptc and Smo transcripts are colocalized in a few areas such as the hippocampal granule cells. However, Ptc transcripts are also observed without any detectable Smo expression, such as in the superior colliculus. These observations suggest that in the adult brain, Shh signals through its receptor complex Ptc/Smo, or through Ptc alone. Ptc protein presents a sterol sensing domain which has been identified in several proteins, including TRC8, recently implicated in hereditary renal carcinoma and which is also expressed as a 2.5-kb transcript in several rat brain areas. Altogether, these results suggest other roles for Shh signalling in postnatal and adult brain than those initially established during early embryonic development.

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